of capillary vessels. From the histological description of the growth as well as from the illustration which accompanies Nauwerck's article it is obvious that he was dealing with a vascularized thyroid rest of the same type as that encountered in the humerus by both Zetkin and Symmers.

The symptomatology of the condition which we have described above bears a close resemblance to that of the multiple myelomata—the occurrence of multiple primary tumors of the bones, particularly those with red marrow, including the skull, vertebræ, ischium, sternum, and ribs; excruciating pain and exquisite tenderness referable to the distribution of the osseous growths; apparent absence of visceral metastasis; regional infiltration of tissues following direct extension from the bone; spontaneous fracture; emaciation and anemia—all are symptoms highly suggestive of the myelomata. The resemblance is not vitiated by the absence of Bence-Jones protein in the urine, for not all cases of myelomata are attended by albumosuria and, moreover, the Bence-Jones protein has been demonstrated in the urine in lesions of the bony system other than myelomatosis.

Histologically the myeloma is a tumor springing from certain cytoblastic constituents of the bone marrow, and is oftenest composed of elements of the type of premyelocytes or of plasma cells. The tumor we have under consideration, however, presents totally different microscopic features in that it commences with overproduction of bloodvessels of the capillary variety and, as a result of continued proliferation of the lining endothelium, brings about distension of the vessel lumen and eventuates in its partial or complete occlusion by tumor cells. At the same time the tumor displays a remarkable tendency to produce subsidiary vascular channels within the lumen of the parent capillary.

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## THE DISTRIBUTION OF TETANUS TOXIN IN THE BODY.

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It has been a matter of common experience ever since the laboratory study of tetanus began that when one injects a sufficient quantity of tetanus toxin into the muscles of the hindleg of a laboratory animal—*e. g.*, guinea-pig or rat—that after a varying period of incubation the injected leg will become stiff and outstretched. Then, generally, the toxin affects in succession the other muscles of the body, first those of the hindleg on the opposite

side, next those of the back, and finally of the neck, thorax, and head. By this time convulsive seizures of increasing severity and with decreasing intervals have appeared, and at last, with asphyxia or exhaustion, death ends the scene. The convulsions are usually spontaneous, but may also be produced by sensory irritation, such as stroking, pinching, or a sudden noise. The inoculated limb, as a rule, remains stiff and outstretched until the moment of death, when it and the remaining muscles of the body become suddenly relaxed and softened, only to stiffen again after the rapid onset of *rigor mortis*.

If the toxin should be injected into other portions of the animal's body—*e. g.*, pleural cavity—instead of into the hindleg the gradual progression of the symptoms would not be so manifest and local or ascending tetanus[1] would appear. Either the muscles of the head and neck would be first attacked and then the remaining muscles in more or less regular succession, so-called tetanus descendens, or the order of the attack would be first local and then general without reference to the contiguity of the muscle groups or nerve centres, so-called mixed or general tetanus. Most of the laboratory animals, by inoculation into the muscles of an extremity, will exhibit local tetanus or tetanus ascendens. Tetanus in man or horses, on the contrary, is more apt to assume the form of tetanus descendens or general tetanus. No matter what may be the order of development, however, the symptoms are always so definitely similar and the clinical picture, as a whole, so unvarying that no argument is necessary to convince one of the specificity of the reaction.

That in natural infections by the tetanus bacillus this organism multiplies locally and elaborates a soluble toxin, which spreads throughout the body, is generally admitted; that the injection of an artificially prepared tetanus toxin into an animal's body in every way corresponds, in the principles governing its action, to the effect of a natural infection, hardly anyone will deny. But as to how this toxin spreads in the system, as to exactly what portions of the body are primarily attacked, and how this process is brought about, are questions which have led to long series of experiments, endless discussion, and many varied and opposing theories. It is not purposed here to discuss in detail all of the opinions which have been offered. For the present it will suffice to mention the more salient features of three important theories and discuss more extensively those which have a direct hearing on my own work and conclusions.

Among the former is the earlier work of Vaillard and Vincent, in which they expressed the belief that local tetanus was due to the direct action of tetanus toxin solely on the muscles themselves. Zupnik later developed and elaborated this assumption. He found

[1] For the accurate classification of these various types of tetanus (ascendens, descendens, and mixed) we are indebted to Zupnik.

that when he injected tetanus toxin into the subcutaneous tissues or into the nerve of an animal's foot at a point where the toxin could not come into contact with muscles the animals were affected by tetanus descendens and not localized tetanus. This latter form did not appear unless the toxin came into close association with muscular tissue, and when this took place those particular muscles were attacked by enduring spasmodic contractures which persisted for a long time and were not released by general anesthesia, curare, or cutting of the corresponding nerve trunks of the muscles. Zupnik attempted also to enervate completely the muscles of an extremity, and, by the injection of tetanus toxin into these muscles, he nevertheless obtained local tetanic spasms. He, therefore, concluded that the muscular phenomena of tetanus arose from direct intoxication of these muscles by the tetanus toxin.

This latter experiment of Zupnik's has been repeated, among others, by Sawamura and Permin, who were both able to show that when an animal's leg has been absolutely separated from all nerve connection with the spinal cord the muscles of that leg will always remain flaccid no matter whether the tetanus toxin be injected into these muscles or into some other part of the body. They believed that, due to faulty or incomplete enervation, Zupnik was able to obtain muscular spasms in the extremity so treated, because these muscles still retained some intact nerve fibers connecting them with the spinal cord. The other portion of Zupnik's evidence, namely, the enduring muscular contraction, requires more detailed consideration. As shown by experiment 8, when an animal dies from acute tetanus, following local injection of tetanus toxin, at the moment of death all the muscles of the body become soft, relaxed, and free from any stiffness or spasm.

Experiment 8.—Guinea-pig No. 3. Weight, 400 gms.

| | | |
|---|---|---|
| Jan. 29, 1915, | 2.30 P.M. | Tetanus toxin,[2] 0.1 c.c. intraperitoneal. |
| Feb. 1, 1915, | 8.00 A.M. | Right leg slightly stiff and extended. |
| Feb. 2, 1915, | 8.00 A.M. | Right leg completely stiff. Beginning stiffness opposite leg. |
| Feb. 3, 1915, | 9.00 A.M. | Rear portion of body entirely stiff and rigid. Spasms in muscles of back and neck. |
| | 12.00 M. | All muscles of body except front legs affected. Respiration rapid. |
| | 5.00 P.M. | Death (five days two and one-half hours). At moment of death entire body including hindquarters soft and freely movable. |
| | 5.05 P.M. | Postmortem rigor, rapidly involving entire body. |

[2] For the tetanus toxin and antitoxin used in these experiments, I am indebted to the kindness of the Hoechst Farbwerke, Hoechst, a. M.

This observation has been repeated many times in mice, rabbits, and rats as well as in guinea-pigs. That the same relaxing effect may follow the administration of certain drugs in the acute stages of tetanus is seen in experiment 94, a portion of whose protocol is given below.

Experiment No. 94.—Rabbit No. 5. Weight, 3090 gms.

| | |
|---|---|
| Mar. 24, 1915, 10.00 A.M. | Tetanus toxin, 0.5 c.c. (right hindleg). |
| Mar. 25, 1915, 10.00 A.M. | No symptoms. |
| Mar. 26, 1915, 8.45 A.M. | Slight stiffness in right hindleg. |
| Mar. 26, 1915, 9.40 A.M. | $MgSO_4$ (25 per cent. sol.), 7 c.c. subcutaneous. |
| 10.10 A.M. | Stiffness entirely disappeared. |
| 6.00 P.M. | Right leg again stiff. $MgSO_4$ (25 per cent. sol.), 8 c.c. subcutaneous. |
| 6.30 P.M. | All stiffness disappeared. |

This experience was repeated a number of times with this rabbit and with other animals, and demonstrated that under the influence of appropriate narcotics all local spasms in acute tetanus may be temporarily removed. The same fact has been shown many times by others in various ways, *e. g.*, by cutting the motor nerves, by ether or chloroform anesthesia, or by injections of cocain or curare, and leaves no doubt that the primary action of tetanus toxin is not on the muscles but is on the spinal cord.

Certain facts, however, which have been observed by almost every laboratory worker on tetanus and which formed a part of the evidence advanced by Zupnik in favor of his theory, remain to be explained. When one produces a local spasmodic contraction in an animal's muscles by injection of tetanus toxin and the animal lives long enough—*i.e.*, does not die with acute tetanus—this spasmodic contraction may become more or less permanent. The following protocol is an example of this frequently observed phenomenon:

Experiment 21.—Guinea-pig No. 17. Weight, 540 gms.

| | |
|---|---|
| Feb. 10, 1915, 12.15 P.M. | Hoechst antitoxin, 1 c.c. (5.2 units[3]) intraperitoneal. |
| 2.15 P.M. | Tetanus toxin, 0.3 c.c. in muscle of right hindleg. |
| Feb. 11, 1915. | Right hindleg extended and stiff. Animal otherwise normal. |
| Feb. 12, 1915. | Stiffness of right leg more pronounced. |
| Feb. 13, 1915. | Entire right hindquarter stiff and board-like. No other muscles affected. |
| Feb. 22, 1915. | Leg atrophied. Foot swollen. Animal runs and eats. |

[3] German standard.

| | |
|---|---|
| Mar. 1, 1915. | Weight, 470 gms. Appears thin. Otherwise the same. |
| Mar. 18, 1915. | Leg movable in foot portion. Swelling reduced. Weight, 500 gms. |
| April 23, 1915. | Leg movable in all portions. Slight stiffness at hip. Weight, 600 gms. (seventy-two days). |

This same condition has also been repeatedly observed in rabbits and rats as well as in guinea-pigs. As has been shown by Goldscheider, Zupnik, Meyer and Ransom, Permin, and others, this sort of spasm does not disappear when the nerves are cut, or when narcotics or magnesium sulphate are given, or even after death. It is a long-enduring and almost inexhaustible stiffness which resists all attempts at passive motion, shows evidences of vascular and trophic alteration (atrophy and edema), and only after weeks and even months does it begin gradually to disappear. If the animal dies or is killed the changes found both grossly and microscopically are only those which might result from long and continuous non-use. Ribbert examined for Meyer and Ransom the spinal cord of a cat which had lived for five months with an unchanged tonic spasm of both hindlegs. He found that most of the ganglion cells of the anterior horns at this level showed degenerative changes. However, it appears probable that such changes are purely secondary, not representing in any way the primary action of the tetanus toxin on either the spinal cord or muscles. Just what combination of chemical changes must occur in order to convert a temporary and easily relaxable muscle spasm into an enduring one is not entirely clear. Gumprecht declared, "Dieser Starre der Muskeln ist nichts anderes als ein hochgradiges Ermuduengs-phaenomen, wie es den Physiologen vom electrischen Tetanus laengst bekannt ist." Meyer and Ransom suggest that such contractions represent a disturbance of the "muscle tonus" centres, which in their inexhaustibility and independence from volition are probably distinct from the motor centres. At any rate it becomes evident that the phenomenon cannot serve as proof for Zupnik's assertion.

The second of the three theories was advanced by Pochhammer who proposed to explain all local phenomena occurring in tetanus by the action of the toxin on the myelin sheaths of the peripheral nerves. According to him the tetanus toxin so alters the myelin that the normal insulation of the nerves is interrupted and "short circuits" may take place, especially in those nerve trunks which contain a mixture of sensory and motor fibers, whereby sensory stimuli pass directly across between the nerve bundles instead of being conducted along the normal reflex arc to the spinal cord. As a partial proof of this hypothesis he treated nerve trunks with ether, thus dissolving the lipoids in the myelin sheaths and producing an artificial "short circuit" which he asserted simulated that con-

dition which occurs in tetanus. This latter experiment was repeated by Permin, who admits that when the nerves are so treated a stiffness of the corresponding limb results; but he concludes that this stiffness is not at all similar to that which is found in tetanus. Sawamura further calls attention to the fact that the direct injection of toxin into the substance of the spinal cord or brain will produce a fatal tetanus. Here a "short circuit" of the peripheral nerves can hardly enter into the question. Moreover, if the tetanus toxin has its primary and sole effect on the peripheral nerves, it becomes difficult to explain, not only the non-neutralizing actions of these nerves when mixed with toxin, as shown by Meyer and Ransom, but also the neutralizing action of the brain-and-cord-toxin mixtures, as demonstrated by Wassermann and Takaki. Not only has Pochhammer's theory received no substantial support from other workers, but it does not explain satisfactorily the various phenomena arising as the result of the inoculation of tetanus toxin.

The third theory received its chief support from Autokratow as well as Courmont and Doyon, who believed that the local spasm resulted from an intoxication of the peripheral sensory nerves alone, so that the supposedly more or less normal motor ganglion cells received intensified sensory impulses and reacted in a correspondingly intensified manner. They based their theory in large part upon the results of the well-known experiment (performed among others also by Goldscheider and Permin) in which, by cutting the posterior (sensory) lumbar nerve roots between the spinal ganglion and the cord, all tetanic spasms in the hindleg of an animal, in consequence of the injection of tetanus toxin, are at once released, if they have been present before the operation, or do not appear in this leg at all. In short, cutting the posterior nerve roots prevents or removes tetanus spasms in the muscles which are supplied by those nerves.

Other workers have endeavored in various ways to show the relation which the sensory nerves and centres bear to the general phenomena of tetanus. Sawamura cut as many as possible of the sensory nerves of the skin of a rabbit's hindleg, thereby producing complete anesthesia, and then injected tetanus toxin into the muscles of that leg. While tetanus symptoms finally appeared in the injected extremity, they were slower in developing and less severe than those caused by the same amount of toxin in an unoperated animal. Meyer and Ransom, on the other hand, injected tetanus toxin into purely sensory nerves such as the nervus infraorbitalis and saw not only an unusually prolonged incubation but also a marked diminution in the severity of the reaction. By still another and more striking experiment they were able to show that motor phenomena alone need not play the major role in the symptomatology of tetanus. After carefully exposing the spinal cord in the lumbar region they uncovered the posterior roots and injected

tetanus toxin into one of these at a point between the lateral ganglion and the spinal cord. The animal developed a peculiar "sensory" type of tetanus, which they called "tetanus dolorosus" and which was characterized by the presence of a marked localized sensitiveness (Schmerzerregbarkeit), which was so extraordinarily pronounced that the slightest contact, even a light blowing on the skin of the affected area, led to a violent, apparently unbearable spasm of pain. These attacks also occurred in the form of paroxysms, interrupted by periods of comparative quiet. Owing to the fact that during these attacks the animal would bite at the affected area and make every effort to alleviate the acute pain, Meyer and Ransom concluded that the reaction represented "brain reflexes, *i. e.*, coördinated defensive movements (Abwehrbewegung)." Motor spasms or the usual muscular phenomena of tetanus were absent, the animal finally succumbing apparently only to exhaustion.

It thus appears clear that the sensory portion of the spinal cord and brain play some role in the production and maintenance of the typical spasms and convulsions of tetanus. One has only to observe closely the extreme sensitiveness to sensory stimuli which is exhibited by most tetanus patients to be convinced of the general application of this statement. To what extent, however, in the usual forms of tetanus there is a direct intoxication of the sensory nerve centres is by no means clear, and certainly it does not seem to be true that under ordinary circumstances the sensory nerves and those alone are affected. Referring again to the fundamental experiment in which is shown the effect on tetanus produced by section of the posterior nerve roots, may be mentioned the work on frogs by Hering, who cut the posterior roots during strychnin poisoning. So long as the motor neurons remained thereby isolated the animal showed no "strychnin convulsions," but on irritation of the central stump the state of increased excitability of the motor segment was at once manifest and typical tetanic spasms ensued. As strychnin admittedly affects the anterior horn cells of the spinal cord, this experiment would tend to show that also in tetanus the sensory fibers in the main merely serve to convey the stimuli necessary to set in operation the motor apparatus—in other words it demonstrates the physiological maxim that the motor ganglion cells do not act purely automatically.

According to Brunner, Goldscheider, Gumprecht, Marie and Morax, Stintzing, Meyer and Ransom, and Sawamura, the spasmodic contraction of the muscles seen in local tetanus results from the action of tetanus toxin on the anterior horn ganglion cells of that portion of the spinal cord governing the muscles of the affected extremity. In their opinion the toxin passes to these ganglion cells by way of the motor nerves, a theory with which most of the writers on experimental tetanus are today in full accord.

Meyer and Ransom, Marie and Morax, and Sawamura contend that this conduction of the toxin must take place along the axis-cylinders, or, as Meyer and Ransom say, "Das Gift muss also im Fibrillenplasma stroemen."

As proof of this contention, Marie and Morax injected tetanus toxin into the hindleg of a guinea-pig and after a definite lapse of time, by killing the animal, cutting out the sciatic nerves and inserting pieces of these under the skin of mice, were able to demonstrate the presence of toxin in the nerves of both legs, particularly in those of the inoculated leg. The blood of these guinea-pigs was also found toxic but not the muscles of the inoculated limb. This diffusion of toxin to the nerves, if they were normal, occurred within one and a half hours. If, however, they had been previously sectioned, twenty-four hours were necessary before any amount of toxin could be demonstrated in the peripheral or distal portion, while if one allowed six or more days to elapse, or until degenerative processes had had time to occur, no toxin at all could be shown to be present. The proximal or central portion of these cut nerves did not contain virus. Even when toxin was injected into other areas, such as the vitreous humor of the eye or the testicle, its presence could still be detected later in the sciatic nerves. If a nerve which had already absorbed toxin was cut this toxin rapidly disappeared from the central portion, and when toxin was injected into the lumbar swelling of the spinal cord it spread upward in the cord but not to the peripheral nerves. From these and similar experiments the authors concluded that the toxin was absorbed by the muscle nerve endings and passed centripetally to the spinal cord by way of the axis-cylinders and not either by nerve sheaths or by lymph channels.

This demonstration of tetanus toxin in the nerve trunks of peripheral nerves following intramuscular injections has been repeated and confirmed many times, among others by Pochhammer, Meyer and Ransom, Sawamura, and Permin. Also the retardation or even complete interruption in toxin absorption, which follows cutting the nerves of an injected limb, has been fully proved. For Meyer and Ransom these facts were sufficient grounds for postulating the condition of tetanus toxin in the axis-cylinders.

However, exception to this current view must be taken so long as it is not better supported. An important theoretical consideration in this connection must be mentioned. While, according to this theory, the toxin is conducted to the spinal cord and throughout the cord itself in the fibrillar structures of the axis-cylinders, both its chemical union and its toxic effect are supposed to take place in the protoplasm of the ganglion cells. This combined assumption is perhaps admissible, but, up to the present time, has not been demonstrated to be true for any other toxic substance. If the axis-cylinders really possess such a marked affinity for toxin

that they can conduct this from the peripheral portions throughout the entire nervous system, the ultimate union with the protoplasm of the ganglion cells appears rather difficult to explain. Meyer and Ransom found that when normal sciatic nerves were cut and brought into contact with tetanus toxin *in vitro* they exhibited no particular power to fix the toxin. From this they concluded that the affinity between tetanus toxin and nerve substance was not the same kind as that which had been demonstrated by Wassermann and Takaki to exist between this toxin and brain or cord substance. But if the axis-cylinder theory holds true there must be some sort of affinity exerted by these structures for the toxin. Can this be denominated as a hitherto unknown "affinity to travel?" The axis-cylinders are an integral part of the ganglion cells, and if the protoplasm of these cells can remove the toxin from their own processes because of a special chemical affinity for it, it is difficult to understand why these cells cannot also take up toxin from the surrounding lymph.

In short, that tetanus toxin travels in the fibrillar substance of a nerve structure without being in any demonstrable manner bound by this substance, and that it is readily delivered to another element of these same structures (ganglion cell body) to form a firm chemical union, rather than that it travels in those paths natural and adapted for the passage to the cells of all substances in a fluid state—namely, in the lymph channels—from a purely theoretical stand-point does not appear to be sound doctrine. On the contrary, it is much easier to explain not only the natural manner of distribution of fluids to the tissues of the body, but also the facts in regard to the distribution of tetanus toxin to the central nervous system by supposing that this takes place by means of the lymph.

Apart from such theoretical considerations, one of the main arguments for toxin conduction by the axis-cylinders—namely, the delay or complete failure in toxin absorption after cutting the nerves—may as reasonably serve to support the conduction-by-lymph theory when attention is directed to the fact that, after cutting the nerves, the myelin sheaths of the peripheral fibers undergo degeneration and their disintegration products can be demonstrated histologically as more or less completely blocking the lymph channels. If it is true, as Gumprecht also asserted, that toxin absorption takes place through the lymph channels, then any paralysis of an extremity must diminish the rate of toxin absorption because of the failure of muscular activity. Also the longer the time which elapses after cutting the nerves, so much more complete will be the stoppage of the lymph channels until any further absoprtion becomes impossible. To the importance of these factors, Aschoff (through Rosenbach) has already called attention in connection with the absorption of adrenalin.

Permin removed the perineurium from a sciatic nerve and found

that, after injection into its peripheral portion, toxin affected the body fully as rapidly as in a normal control animal. But in concluding from this experiment that the toxin must travel in the nerve substance itself and not in the lymph passages he overlooked the fact that countless other lymph channels, aside from those in the perineurium, course freely in the nerve trunks themselves.

Further evidence, however, remains to be explained. Meyer and Ransom, whose really brilliant work on experimental tetanus has done so much to clear up many mooted points in our knowledge of this disease, and who have been very active supporters of the "axis-cylinder conduction theory," carried out the following experiment: A rabbit was treated with tetanus toxin and highly immunized until a test of its blood showed that 1 c.c. held one-tenth antitoxin unit of 4,000,000 −Ms.[4] A large dose of tetanus toxin (5000 +Ms.) was injected subcutaneously without effect. Then in the left sciatic nerve a very small second dose of toxin (200 +Ms.) was injected and the animal on the following day showed severe tetanic spasms, particularly in the muscles of the left leg. A test of the blood removed at this time showed the antitoxin content unchanged. Tests of the cerebrospinal fluid and of the nerve lymph also showed the presence of antitoxin but "much less than the blood." Permin, who repeated and confirmed these results, also proved that a similar reaction can be obtained in an even simpler manner by injecting the antitoxin into the blood stream of a rabbit or dog and shortly after by an injection of toxin into the muscles of the hindleg, whereby a local tetanus ensues which is confined to the muscles of the inoculated leg. In my experiments on rats and guinea-pigs with the prophylactic application of antitoxin I have encountered the same phenomenon, namely, after the injection of concentrated toxin into the muscles of a passively immunized animal, local tetanus of the muscles of the injected leg would appear. Often this stiffness also affected the back muscles of the corresponding hindquarter, but, unless the dose of toxin was overwhelmingly large, this condition did not spread any further and did not endanger the life of the animal.

The possibility, then, must be admitted that tetanus toxin may travel along a nerve trunk to the spinal cord in the body of an actively or passively highly immunized animal, from which fact Meyer and Ransom concluded that the toxin in its passage along the nerves is not conducted in the lymph but, as quoted above,

[4] The antitetanus serum unit, established by Behring and used to measure the potency of German serums, represents that amount which will protect one gram of mouse weight against 40,000,000 lethal doses of toxin. A unit lethal dose of toxin for 1 gram of mouse weight is denoted by the sign +Ms. The designation −Ms. refers to the amount of serum necessary to save 1 gram of mouse weight from the fatal effect of a unit lethal dose of toxin (1 +Ms.). Hence 1 A.E. (antitoxin einheiten) or unit represents 40,000,000 −Ms.

"Das Gift muss also im Fibrillenplasma stroemen." Permin from the same fact drew a similar conclusion, namely, that the experiment demonstrates that the nerve substance itself must be regarded as the conducting medium. This conclusion does not seem to be fully justified, and I believe that the facts can be better explained by the "lymph channel theory." Following injections of toxin, tetanic symptoms are produced simply because the tetanus toxin is concentrated enough to more than neutralize the antitoxin present and thereby can pass through the lymph channels to varying distances up the spinal cord before it is rendered harmless by the circulating antitoxin or is fixed by the nervous tissue.

When Meyer and Ransom and also Sawamura injected tetanus antitoxin into a nerve trunk they found that this particular nerve and its corresponding nerve segment were fully protected from the action of the following injection of tetanus toxin, no matter whether this toxin was injected directly into the same nerve or into some neutral area. In other words, they provided antitoxin in sufficient local concentration to neutralize an equally or less locally concentrated toxin.

Ransom has shown that in whatever manner either tetanus toxin or antitoxin may be injected into the body, they both shortly appear in the blood stream and thence in the lymph. The antitoxin apparently remains in the blood and the lymph until its final disappearance from the body, while the toxin is largely taken up by the nerves, conveyed to the cord and brain, and there fixed in the protoplasm of the ganglion cells. However, it seems well established that the lymph channels of the body, apart from the site of injection, never contain antitoxin in very concentrated amounts and this appears to be equally true of the lymph spaces of the central nervous system. Indeed, Meyer and Ransom assert that antitoxin does not enter the central nervous system by way of the blood and lymph streams, an opinion which perhaps expresses too strongly the *paucity of concentrated antitoxin* in that part of the body for later in the same paper (p. 413), in discussing the researches of Roux and Borrel, who were able to produce tetanus in highly passively and also actively immunized dogs by injections of toxin into the cerebral substance, Meyer and Ransom suggested that "the toxin concentrated at the site of injection could not be at once neutralized by the antitoxin which was certainly present in the centres although in low concentration, and consequently, enough time elapsed in which to poison the nerve cells before sufficient additional antitoxin-laden blood appeared; we have to deal, then, with a regional difference of concentration." This condition of affairs also maintains when concentrated toxin is injected in or near a nerve trunk, and the facts brought forth in this connection cannot serve as arguments in favor of the conduction of tetanus toxin along the axis-cylinders.

On the contrary, the evidence so far presented by the numerous workers is distinctly in favor of the theory which designates the lymph channels as the natural medium of exchange for fluids between the different portions of the body, including the central nervous system.

The chief supporters of this latter view have been Gumprecht and Stintzing, the last named having reported the presence of tatanus toxin in the cerebrospinal fluid of two human cases of tetanus. This finding has not been sufficiently confirmed either in cases in men[5] or by animal experimentation (Ransom). I have tested on white mice the cerebrospinal fluid from two severe fatal cases of tetanus and was unable to prove the presence of tetanus toxin. Gumprecht's conclusions, on the other hand, were based on purely experimental grounds. He injected tetanus toxin into the subdural space of the lumbar cord and found that tetanus appeared first in that extremity corresponding to the side on which the injection was made. He called attention to the injection experiments of Key and Retzius, who, by means of Berlin blue and gelatin (Richardson's blue), found that not only are the peripheral nerves and spinal cord full of intercommunicating lymph channels, so rich that even each individual fiber is surrounded, but also that everywhere along the cord are free communications with the subarachnoidal lymph spaces, which spaces in turn freely open into the lymph channels of the perineurium. Therefore Gumprecht stated that "after injection into the hindleg the toxin readily ascends in the numerous lymph spaces of the nerves and on reaching the spinal cord is diffused both up and down (in the cord)."

I have repeated in part Key and Retizius's injection experiments, and have found that by injecting the sciatic nerve a short distance below the spinal ganglion with Richardson's blue the fluid passes freely through the ganglion toward the cord along the motor roots. The lymph channels of the sensory roots are either not injected at all or injected with difficulty by this means. Neither does there appear to be such free communication between the endoneural spaces and the subarachnoid spaces as Key and Retizius indicated, for when the injecting needle is kept in the central portions of the nerves the fluid mass remains within the nerve sheaths and does not invade the arachnoid unless rupture from undue force occurs. The point is of some importance, as it not only explains why tetanus toxin under ordinary circumstances does not pass into the cerebrospinal fluid, and thus why Stintzing's observations have not been fully confirmed, but also it perhaps gives a hint as to why the usual type of tetanus is a motor tetanus and not "tetanus dolorosus," as obtained by Meyer and Ransom when they injected

[5] While most workers report uniformly negative results it should be noted that Permin claims to have demonstrated tetanus toxin in the cerebrospinal fluid of five human cases.

toxin into the posterior roots. In other words, the toxin by following the lymph channels passes first to the motor side of the cord.

Meyer and Ransom repeated Gumprecht's experiment of injecting tetanus toxin into the subdural spaces and confirmed his results. However, while Gumprecht believed that the toxin passed directly by means of the perivascular spaces to that portion of the spinal cord with which it first came into contact, on the other hand, Meyer and Ransom concluded that it was first absorbed into the blood stream, taken up by the peripheral nerves, and thus conveyed in the usual manner to the spinal cord, where that part which had been injured by the injection, a *locus minoris resistentiae*, would be the first affected. This hypothetic injury, they believed, was impossible to avoid.

It is necessary to note here an experiment of Permin, whose views, as stated, are in full accord with those of Meyer and Ransom. After injecting tetanus toxin into the muscles of the hindlegs of rabbits, and at the same time antitoxin into the blood stream (to prevent general tetanus), he injected antitoxin intraspinally at varying intervals of time. Such injections had to be made within at least four hours after the injection of the toxin in order to prevent the outbreak of a local tetanus. Permin does not explain how this result was accomplished, but it is reasonable to suppose that the antitoxin passes into the lymph channels of the nerve roots and there neutralizes the ascending toxin which must also be in the nerve lymph. From this experiment he rightly concludes that the conduction of toxin in the nerves must proceed with extraordinary rapidity (p. 24), a fact which is well explained by the rapid movement of lymph in the nerve sheaths. Pochhammer, in support of his theory after injecting tetanus toxin into the leg muscles of rabbits, killed the animals, cut out the corresponding sciatic nerves, and, dividing them into three parts, placed each piece under the skin of mice. He found that the peripheral portions of these nerves always held more toxin than the central portions. Sawamura fully confirmed these observations, which also agree with Meyer and Ransom's experiment, in which they found that after cutting a nerve holding toxin this toxin rapidly disappeared from the central or proximal end. While the conclusions derived from these various experiments were different and even contradictory, the results seem to be in full accord with the theory of tetanus toxin conduction by nerve lymph channels. This conduction naturally is slower in the finely divided distal nerve branches, but as the larger nerve trunks are reached and the lymph finds wider spaces through which to travel, the speed is accelerated and not only does the toxin spread faster but it is more diluted by the inflowing lymph currents and can thus more readily be neutralized by the less concentrated antitoxin. It is not possible to explain all these facts by the axis-cylinder conduction theory.

One further expriement was suggested by Professor Aschoff which might throw more light on the subject. This experiment is based

upon the theory that if tetanus toxin is conveyed by the axis-cylinders of the peripheral nerves to the spinal cord, it must also pass up the cord by the same means, while if conveyed to the cord by the lymph channels it must likewise spread by means of the lymph channels. But the spreading of toxin by means of the lymph channels can be prevented by a previous administration of antitoxin, which same, on the other hand, should not prevent the passage of toxin along the axis-cylinders. Hence, if toxin be injected into the lower end of the spinal-cord substance of a passively immunized animal, the manner in which the animal reacts should furnish decisive evidence in favor of one or the other contention. The protocols of these experiments are as follows:

Guinea-pig No. 38. Weight, 350 gms.

April 20, 1915. 1 c.c. tetanus antitoxin, subcutaneous. Twenty-four hours later, under ether anesthesia, the lower portion of the back was prepared for a surgical operation. Through a 5 cm. longitudinal skin incision the fascia and muscles were cut away and by sharp-pointed scissors the spinous processes and posterior portions of the lowest lumbar and upper sacral vertebræ removed, thus exposing the terminal portion of the sacral and lower lumbar cord. Into this exposed cord by means of a fine needle, inserted as far up as possible, 0.1 c.c. of tetanus toxin slowly injected.[6] The needle left in place a few minutes and then slowly removed. Muscles and fascia then carefully brought together by sutures, the skin sewed and the wound covered with an iodoform-collodion dressing. One-half hour later the guinea-pig runs about and is apparently normal in all its movements. On following day there was some distention of bladder by retained urine, which is relieved by gentle pressure on lower abdomen. No tetanic symptoms. Animal eats and runs about in normal manner. Forty-eight hours later the condition was the same. Bladder paralysis has disappeared. Ninety-six hours later there were no symptoms of tetanus or infection of wound.

Control. Rat No. 59. Weight, about 150 gms. Tetanus toxin, 0.003 c.c. in left hindleg. Forty-eight hours later there was marked local tetanus in the left hindleg.

[6] As can be seen by the control experiment this dose was about fourteen times that which would produce tetanus symptoms in the same weight of rat body.

Guinea-pig No. 25.

Mar. 26, 1915. Antitoxin, 0.4 in left hindleg. Five hours later, antitoxin, 0.1 c.c. again in left hindleg.

Mar. 27, 1915. Spinal column and outer end of spinal canal exposed through opening in dura. Toxin, 0.02 c.c. injected into canal.

Mar. 28, 1915. General condition good. Runs about and eats. Bladder and rectum paralyzed.

Mar. 29, 1915. Condition the same. No signs of tetanus.

Mar. 31, 1915. Weaker. Animal killed by ether. No evidence of tetanus. Autopsy: bladder markedly distended. Kidneys show hydronephrosis. Wound clean.

Guinea-pig No. 39. Weight, 500 gms; pregnant.

April 20, 1915. Tetanus antitoxin, 1 c.c., subcutaneous.

April 27, 1915. Injection repeated.

April 28, 1915. The same operation as in No. 38 only slightly higher up and 0.15 c.c. toxin injected into the spinal cord. Animal recovered from operation. Bladder paralyzed. (Control rat died at end of five days). Animal became weaker and without showing the slightest symptom of tetanus was killed after six days. Autopsy showed dead fœti. Wound clean.

Guinea-pig No. 41.

May 6, 1915, 8.00 A.M. Tetanus antitoxin, 1 c.c. in left hindleg.

10.30 A.M. Same operation on spinal column as described above and 0.2 c.c. tetanus toxin injected into the spinal cord.

11.00 A.M. Animal recovered from operation. Eats and runs about.

6.00 P.M. Slight stiffness in hindleg.

May 7, 1915, 10.00 A.M. No further evidences of tetanus. Twenty-six hours after operation animal died suddenly.

12.50 P.M. Autopsy: hemorrhages and pneumonia in both lungs. Spinal cord swollen and moist.

Guinea-pig No. 42.

May 10, 1915. 1 c.c. tetanus antitoxin, subcutaneous. After twenty-four hours, operation as described above and injection of 0.2 c.c. tetanus toxin. No trace of paralysis or tetanus at any time. Control rat dead from typical tetanus after two and one-half days.

These experiments demonstrate that by the injection of tetanus toxin into the lower end of the spinal cord of a passively immunized

animal, this toxin, even in doses which were sufficient to provoke symptoms in control animals, neither produced any marked local effect nor advanced in the spinal cord toward the more sensitive centres of the medulla, in short, that it was not taken up by the axis-cylinders but was prevented by antitoxin from spreading along its natural and customary route, namely, the lymph channels. The experiment moreover confirms in another manner the observation already noted on the occurrence of local tetanus when toxin is injected into the sciatic nerve or into the muscles of an animal's hindleg. In the presence of antitoxin in the system, tetanus toxin, whether injected into the hindleg or into the lower end of the cord does not travel far in the cord, because manifestly as it become more diluted, the antitoxin which is present in the lymph spaces of the spinal cord as well as in the lymph channels of the nerves has an opportunity to neutralize fully the less concentrated toxin and thus protect the portion of the nervous system lying above. The efficiency of this protection is exactly in proportion to the concentration of the antitoxin as compared with that of the toxin.

The objection raised by Permin that if toxin is transported in the lymph spaces of the spinal cord it would be difficult to explain the marked local tetanus which occurs when the leg of an immunized animal has been injected with toxin, does not assume so much weight when we take into consideration the fact that the concentrated toxin passes to the cord by definite lymph channels which are more or less closed until they reach the widely spreading spaces of the cord itself.

I have developed this theme at some length, believing it to be not only of theoretical but also of more than ordinary practical importance. Prophylactic or therapeutic methods in the rational treatment of any disease must be based, as far as possible, upon our knowledge of the causes of this disease and the manner of operation of these causes in the body. Hence in tetanus: if we assume that the path of attack of the toxin in the central nervous system is the axis-cylinders of the cerebrospinal nerves, then our plans for both prevention and treatment should be considerably different from those which should be adopted, if we believed the toxin to be distributed to the ganglion cells by the lymph stream. Terminal nerve fibrils are abundant over especially the entire tegumentary and muscular portions of the body. If they possess for tetanus toxin a "conductive affinity," then, in spite of all we may hope to accomplish even by prophylaxis, without complete enervation of the local area where the toxin is elaborated, the absorption by these fibrils of toxin before it can possibly be neutralized and the subsequent intoxication of corresponding nerve centres cannot be prevented by any means which, at present, is at our command. Antitoxin, admittedly, does not travel in the

nerve fibrils but in the lymph channels, and hence the passage of toxin, on the basis of the above theory, cannot be interrupted.

However, it would appear more reasonable to assume that tetanus toxins, just as other poisons, pass throughout the body exclusively by the blood and lymph streams and, theoretically, may be neutralized by antitoxin and at any stage in this passage before the final and comparatively indissoluble union with the ganglion cells occurs. The practical difficulties associated with neutralizing, by injections of antitetanus serum, the toxin already in the nerve trunks, in cases of outbroken tetanus, have been discussed in a previous paper.[7] But assuming the lymph-conduction theory to be true, these problems, however practically insurmountable they may be at the present time, are still capable theoretically of solution, and no doubt in the future some method may be found for the immediate protection of threatened nerve cells and perhaps even the saving of those already attacked. At least the situation is by no means hopeless.

In this connection may be seen the rationality of Behring's early endeavors to obtain a highly potent antitetanus serum, a serum so concentrated that, diluted as it must be by all the tissue fluids of the body, when it comes into contact with toxin it shall possess enough "neutralizing mass" to meet and overcomes this toxin, before the vital centres can be affected.

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## STUDIES ON A CASE OF IDIOPATHIC PURPURA HEMORRHAGICA.

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Purpura hemorrhagica is a condition that is characterized in its severer forms by hemorrhage from the mucous membranes, petechiæ or ecchymoses of the skin, a markedly reduced platelet count, a much prolonged bleeding time and non-retractile blood clot. A normal or somewhat delayed coagulation time occurs.

In its milder form there may be but ecchymoses following injury or excessive bleeding from some local cause; the other characteristics mentioned above, though present, are not so extreme. In this country, Duke[1,2] especially has studied this condition.

This form of purpura, though often not clearly differentiated in the literature from other types of purpura and hemorrhagic disease, can be easily distinguished from them, because in these conditions there is no reduction of the platelet count.

Purpura hemorrhagica may occur as an idiopathic disease, though more frequently perhaps as a symptom complicating various diseases, especially aplastic anemia, leukemia, tuberculosis, nephritis, etc. A congenital idiopathic type exists.

Case Report. Various studies on a case of the idiopathic type which died in spite of eleven transfusions of blood are presented

[1] Arch. Int. Med., 1912, x, 445. [2] Jour. Am. Med. Assn., 1910, lv, 1185.